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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

ASTRAZENECA AB; AKTIEBOLAGET HÄSSLE; ASTRAZENECA LP; KBI INC.; and KBI-E INC., Plaintiffs and Counterclaim-Defendants, v. HANMI USA, INC., HANMI PHARMACEUTICAL CO., LTD., HANMI FINE CHEMICAL CO., LTD, and HANMI HOLDINGS CO., LTD., Defendants and Counterclaim-Plaintiffs.	Civil Action No. 3:11-CV-00760-JAP-TJB Judge Joel A. Pisano Magistrate Judge Tonianne J. Bongiovanni ATTORNEY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER FILED UNDER SEAL

ASTRAZENECA'S REPLY *MARKMAN* BRIEF

Pursuant to the Court's March 1, 2012 Letter Order (D.I. 206), AstraZeneca submits this reply brief in response to newly disclosed positions and evidence presented in Hanmi's responsive *Markman* submissions.

Hanmi asserts that AstraZeneca's construction of the '504 patent claim term, "alkaline salt" of esomeprazole, includes toxic salts. In asserting this new position, Hanmi takes out of context certain statements made by AstraZeneca and AstraZeneca's expert, Dr. Davies. As explained below, consideration of these statements in their proper context makes clear that AstraZeneca has never taken a position that toxic salts are among the salts in the '504 patent claims. In fact, the parties are in agreement that such a construction would be inconsistent with the understanding of a person of ordinary skill in the art.

Hanmi also newly asserts that a person of ordinary skill would expect esomeprazole to be compatible with acidic conditions and thus would not exclude acid addition salts from the scope of the '192 patent claim term, "pharmaceutically acceptable salt" of esomeprazole. However, for support, Hanmi points only to prior art patents that are silent as to the stability of omeprazole (or its enantiomers) under acidic conditions, and that do not exemplify any acid addition salts of omeprazole (or its enantiomers). In selecting this art, Hanmi has also ignored clear statements in prior art previously cited by both parties that would have led a person of ordinary skill to conclude that *esomeprazole is* incompatible with acidic conditions.

Hanmi's new positions are therefore without merit.[1]

[1] References are provided herein to AstraZeneca's opening *Markman* brief ("AZ Br."; D.I. 133.0), Hanmi's responsive *Markman* brief ("Hanmi R. Br."; D.I. 174.0), Patrick L. Chen's Nov. 7, 2011 declaration ("Chen"; D.I. 133.1-2), Michael E. Furrow's Jan. 6, 2012 declaration ("Furrow"; D.I. 176.1-3, 177.0-3); Renita S. Rathinam's Jan. 6, 2012 declaration ("Rathinam"; D.I. 175.0-5, 179.0-10); Dr. Stephen G. Davies' Nov. 7, 2011 declaration ("Davies"; D.I. 133.3-5), Dr. Jerry L. Atwood's Jan. 6, 2012 supplemental

I. AstraZeneca's Proposed Construction of "Alkaline Salt" of Esomeprazole in '504 Patent Claims 1, 2, 4, 6 and 7 Does Not Embrace Toxic Salts

AstraZeneca's proposed construction for "alkaline salt" of esomeprazole in the claims of the '504 patent is "a basic salt (here, a salt in which (–)-omeprazole is negatively charged) *that is suitable for use in a pharmaceutical formulation*." (Emphasis added.) For support, AstraZeneca has cited, *inter alia*, the '504 patent claims, which are directed to pharmaceutical formulations and methods of treatment, as well as the '504 patent specification, from which the medical utility is clear. (AZ Br. 17–18). *See, e.g.*, *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (a claim term is to be construed "in the context of the particular claim in which the disputed term appears, [and] the entire patent"). From the proposed construction, and the pharmaceutical context provided by the claims and specification specifically called out by AstraZeneca, it should be clear that AstraZeneca did not propose that the claimed "alkaline salts" of esomeprazole include toxic salts—such a construction would be unreasonable. *See, e.g.*, *Mitsubishi Chem. Corp. v. Barr Labs., Inc.*, 435 Fed.Appx. 927, 934–35 (Fed. Cir. 2011) (In "[c]laims to 'pharmaceutical compositions' . . . [e]ach of the constituent parts of the composition must be pharmaceutically acceptable . . . .").

Nevertheless, Hanmi, in its responsive *Markman* brief and accompanying supplemental declaration of Dr. Atwood, asserts that AstraZeneca's construction embraces toxic salts, and offers new evidence ostensibly to rebut that construction. Hanmi's misunderstanding appears to be the result of reading certain statements made by AstraZeneca and its chemistry expert, Dr. Davies, out of context.

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declaration ("Atwood Supp."; D.I. 174.1); and to the supplemental declaration of Dr. Stephen G. Davies submitted herewith ("Davies Supp.").

In AstraZeneca's opening *Markman* brief, AstraZeneca explained that an "alkaline salt," as a general concept, is simply a "basic salt"—"alkaline" meaning "basic." This was provided as background, and was supported by the testimony of Dr. Davies and a page from a contemporaneous dictionary that included definitions of "alkali metals" and "alkaline earth metals" (which generate basic solutions in water), and "alkalinity" and "alkaline solution" (which simply require that the solution in question be basic). However, each general explanation was followed by a clarification that *given the pharmaceutical context provided by the claims and the specification* of the '504 patent, only pharmaceutically acceptable alkaline salts of esomeprazole are covered by the claims. (AZ Br. 7–8; Davies ¶¶ 36, 41, 51, Exh. 2; Davies Supp. ¶¶ 3–16).

Dr. Davies reemphasized the importance of the context provided by the '504 patent to the construction of "alkaline salt" at his deposition:

> Q: But in no claim is the alkaline salt described as 'pharmaceutical' or 'pharmaceutically acceptable[,]' [i]s that correct?
>
> A: Well, it would have to be—or else it wouldn't be in a pharmaceutical formulation."

(Furrow Exh. 1 at 64:3–8). Hanmi ignores this evidence when it misinterprets a subsequent statement by Dr. Davies that "all alkaline salts fulfill the criteria covered by the patent" as indicating that AstraZeneca's construction embraces toxic salts. But, not only did Dr. Davies explain his position earlier in his deposition, he also made clear, in response to the question immediately following the answer that Hanmi relies on, that salts of esomeprazole are covered by the claims only "if they fulfill the other—all the other criteria of the '504 patent." (*Id*. at 172:18–22; *see also* 173:21–24). And, the subsequent question reveals that, at least at the time of the deposition, Hanmi fully understood AstraZeneca's and Dr. Davies' position that the claimed salts were pharmaceutically acceptable:

> Q: Would a person of skill in the art understand that the titanium salt of the (–)-enantiomer of omeprazole would have properties sufficient to make it pharmaceutically acceptable, as you've explained is part of the '504 patent claims?

(*Id.* at 172:23 to 173:2). Dr. Davies has responded to Hanmi's misinterpretation of his testimony in his supplemental declaration accompanying this brief. (Davies Supp. ¶¶ 3–22).

In light of the foregoing, Hanmi's new evidence addresses a construction that is not before the Court; the Parties are in agreement that it would be unreasonable to interpret this claim term as covering toxic salts. (*See* Hanmi R. Br. 4; Atwood Supp. ¶¶ 15–23; Davies Supp. ¶¶ 3–22).

Given the proper understanding of AstraZeneca's proposed construction, Hanmi's newly articulated concerns about the ability of one skilled in the art to identify and prepare *all possible alkaline salts* of esomeprazole are inapposite. Indeed, as previously noted (D.I. 92.1, Exh. A at 1; D.I. 189 at 2; Davies ¶¶ 42 fn. 3, 54, 55), a person of ordinary skill would have been able to readily identify, for example, at least the six exemplary cations in the '504 patent; the additional cation in prior patents directed to "alkaline salts" of omeprazole (Davies Exhs. 6 and 7); the 21 cations known to be fit for human consumption identified in the Berge reference (D.I. 112-4 at 2–3); and references reporting the pharmaceutical suitability of strontium salts (Davies Exhs. 3–5).[2] And the person of ordinary skill would not consider toxic salts. The universe of

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[2] Hanmi now contends that the strontium references "say nothing about whether any of the compounds disclosed are suitable for use in a pharmaceutical formulation." This assertion flies in the face of express statements in these references (*see, e.g.*, Davies Exh. 5 at 547: "strontium (Sr) at low dosage levels has been proposed to be of therapeutic value in patients with osteoporosis"), and of Hanmi's citation of the very same references [redacted] to the Patent Office in its own patent (*see* D.I. 190, Exh. F at col. 2, ll. 49–52: "strontium exerts no safety problems even at a dose of 633/mg/kg/day in rats," citing one of the same articles). (Davies Supp. ¶ 28).

possible salts is thus far less than the "hundreds of thousands" of salts (Atwood Supp. ¶ 12) that Hanmi mistakenly asserts AstraZeneca's construction to embrace.[3] (Davies Supp. ¶¶ 23–42).

II. Hanmi's New Evidence Does Not Rebut the Clear Statements in the Intrinsic Evidence and Prior Art that Would Have Led a Person of Ordinary Skill to Conclude that Esomeprazole Is Incompatible with Acidic Conditions

AstraZeneca's construction of "pharmaceutically acceptable salt" of esomeprazole in the method of administration claims of the '192 patent is commensurate in scope with the "alkaline salt" of esomeprazole in the '504 patent claims. For support, AstraZeneca has cited (D.I. 92.1, Exh. C pages 3–4; AZ Br. 17–18; Davies ¶¶ 63–67) column 1 of the'192 patent that incorporates the "salt forms of the single enantiomers of omeprazole" from the '504 patent (Chen Exh. 2, col. 1, ll. 10–13); the '504 patent where it states that "acidic conditions" would be "devastating" for the individual enantiomers of omeprazole (Chen Exh. 1, col. 1, ll. 27–42); the declaration of Dr. Andersson from the '504 patent file history characterizing the enantiomers of omeprazole as "acid labile" (Chen Exh. 4 at AZ0005000175); and AstraZeneca's U.S. Patent No. 4,738,974 patent and European Patent No. 0 124 495 that state that omeprazole is "susceptible to degradation in acid" (Davies Exh. 6 at 6, Exh. 7 at col. 4, ll. 25–30). (Davies Supp. ¶¶ 43–49, 62). Hanmi identified this same evidence in support of its proposed construction. (D.I. 92.1, Exh. D at 1–3).[4]

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[3] While some salts may need to be prepared to determine whether they meet the various limitations of the claims (*e.g.*, "substantially crystalline form"), that has no bearing on the remaining claim construction disputes or the validity of the claims. *See*, *e.g.*, *Enzo Biochem, Inc. v. Applera Corp.*, 599 F.3d 1325, 1336 (Fed. Cir. 2010) ("The claims are not indefinite even if some experimentation is required to determine the exact [scope]."); *Exxon Res. Eng'g Co. v. U.S.*, 265 F.3d 1371, 1379 (Fed. Cir. 2001) ("Provided that the claims are enabled, and no undue experimentation is required, the fact that some experimentation may be necessary to determine the scope of the claims does not render the claims indefinite.").

[4] [redacted]

Now, however, Hanmi asserts that a person of ordinary skill would have considered esomeprazole to be compatible with acidic conditions. As explained by Dr. Davies, Hanmi's evidence fails to support this position.

Hanmi newly cites two prior art patents, U.S. Patent Nos. 4,337,257 and 5,066,652 (the " '257 patent" and " '652 patent," respectively) in support of this proposition. The '257 patent, however, simply defines a genus of many millions of compounds and states that "neutral"/"free base" forms may be prepared, or "acid addition" or "basic" salts, "depending on the process conditions." (Rathinam Exh. 9 at col. 2–3, 5). Nowhere does it provide a specific identification or exemplification of omeprazole (or one of its enantiomers) or any specific salt thereof, or any discussion of the behavior of omeprazole in the presence of acid. The '652 patent also defines a genus that embraces many millions of compounds and similarly says nothing about the compatibility of omeprazole with acid. (Rathinam Exh. 10 at col. 1–2). These patents therefore would not inform the perspective of a person of ordinary skill as to the acid stability or instability of omeprazole or its enantiomers. (Davies Supp. ¶¶ 50–52).

Hanmi also cites to a prior art abandoned German patent application, DE 4,035,455 ("DE '455"), which Hanmi asserts exemplifies the preparation of the (+)-enantiomer of omeprazole in high optical purity under acidic conditions. However, as Dr. Davies explains, it is not possible to assess the chemical and optical purity of the (+)-omeprazole reported in this reference based on the disclosure alone. Moreover, the optical and chemical purity of the (+)-omeprazole actually reported in DE '455 has been the subject of various proceedings involving the patents-in-suit or foreign equivalents thereof around the world. Evidence that has been presented on the DE '455 example includes testimony of the DE '455 inventors regarding the

[redacted]

actual experiment that is reported in DE '455; testimony of AstraZeneca scientists who attempted to reproduce the DE '455 example back in 1993 for purposes of generating material for toxicity studies. Dr. Davies has previously considered this evidence, and has explained that it supports the conclusion that the DE '455 process provided (and provides) low yield of (+)-omeprazole in low chemical and optical purity.[5] (Davies Supp. ¶¶ 55–61).

In light of the foregoing, Hanmi's conclusion that prior art patents "clearly establish the existence of acid addition salts" of omeprazole (Atwood Supp. ¶¶ 53–56) and that the "literature is replete with examples of acid salts of omeprazole" (Hanmi R. Br. 17) is without support.[6]

CONCLUSION

For the foregoing reasons, AstraZeneca respectfully requests that the Court adopt AstraZeneca's proposed constructions of the claim terms in dispute, as set forth in AstraZeneca's prior *Markman* submissions in this action.

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[5] Hanmi has been aware of the DE '455 evidence and of Dr. Davies' views thereon since at least the July 25, 2011 service of AstraZeneca's initial responses to Hanmi's invalidity contentions. (D.I. 113.2). Nevertheless Hanmi elected not to address any of it when asserting that "the (+)-enantiomer was obtained" in high optical purity by the DE '455 method. (Atwood Supp. ¶¶ 50, 51).

[6] Hanmi also cites to two non-prior art references, U.S. Patent No. 6,255,502 (earliest priority date, 1996, issued, 2001) and a 2010 article by Karthikeyan. These, of course, cannot inform the claim construction inquiry, *Phillips*, 415 F.3d at 1312–13 (claims are construed as of the effective filing date of the patent application), but they also would not change the understanding of one skilled in the art. The '502 patent lists over a hundred "basic compounds" as possible options from which to prepare the acid addition salts of the invention, and omeprazole is included on that list. However, again, no specific salt of omeprazole is anywhere described or exemplified, and no discussion is given to the stability of omeprazole in the presence of acid. The Karthikeyan article references the hydrochloride salt of omeprazole, but makes no mention of its stability or chemical purity—without which it would not be understood to contradict the prior art teachings discussed above. (Davies Supp. ¶¶ 53–54).

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on March 19, 2012, I caused a copy of the foregoing ASTRAZENECA'S REPLY *MARKMAN* BRIEF and supporting documents to be served upon the following counsel by operation of the Court's electronic filing system and/or electronic mail:

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